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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,354	11/25/2003	Patrick L. Iversen	50450-8311.US03	8250

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EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,354	IVERSEN, PATRICK L.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Amendment

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/2007 has been entered.

2. Claims 1-30 are cancelled. New claims 31-47 are presently pending for examination

Response to Arguments

3. Applicant's arguments with respect to claims 1-4, 13-15 and 25-30 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 31-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter)

6. New Claim 31 recites the following:

31. (New) A method of ***altering*** the pharmacokinetics of ***a drug*** in a subject, comprising:

co-administering with ***a drug*** metabolized by a drug-metabolizing mammalian cytochrome p450 enzyme an effective amount of a morpholino antisense oligomer having a backbone composed of phosphorodiamidate linkages, wherein the antisense oligomer blocks expression of the mammalian cytochrome p450 enzyme.

The scope of the claim as now amended includes a method of altering, it is noted that the term "altering," encompasses both increasing and decreasing the pharmacokinetics of *a drug*, any drug, wherein the drug recited in the pre-amble of the claim is not limited to *a drug-metabolized by a mammalian cytochrome p450 enzyme.* However, the method step recites only that *a drug metabolized by a cytochrome p450 enzyme and a morpholino antisense oligomer that blocks expression of the mammalian cytochrome p450 enzyme are co-administered..*

Applicants do not provide support for a method comprising both the increase and decrease of the pharmacokinetics of any drug is achieved, wherein the method comprises the co-administration of any mammalian cytochrome p450 enzyme, and an antisense oligomer that blocks the expression of the mammalian cytochrome p450.

See MPEP § 714.02 and § 2163.06 ("Applicant should * * * specifically point out the support for any amendments made to the disclosure.").

7. Claims 31-35, 39-43 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

The instant claims read on a method of altering the pharmacokinetics of a drug in a subject, and a method for inhibiting the expression of any drug-metabolizing mammalian cytochrome p450 metabolism in a subject. First, the breadth of the claims comprises a method wherein any aspect of the pharmacokinetics or a drug is changed in any way, wherein the change is associated with the co-administration of a drug with a morpholino antisense oligomer that blocks the expression of mammalian cytochrome p450 enzyme. Secondly, the breadth of the instant claims reads on the inhibition of any form of mammalian cytochrome p450 enzymes, wherein said cytochrome P450 enzymes are isolated from any mammal, and wherein the scope of the enzymes encompasses all other allelic and polymorphic variants of mammalian cytochrome P450 enzymes.

Other than the antisense oligonucleotides targeting CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYPC19, CYP2D6, CYP2E1, CYP3A2, and CYP3A4, Applicants have not shown possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. No guidance is given in the specification as filed that would allow one of skill in the art to predict the structures of any other composition comprising antisense oligonucleotides possessing the claimed

properties, since it is unknown what properties, structural or otherwise, that the antisense oligonucleotides of the present invention must possess for it to reduce the synthesis of a drug metabolizing cytochrome P450 enzyme that reduces the effectiveness of a drug.

Moreover, Applicants were not in possession of the full scope of molecules encompassed by the instant claims at the time of filing of the instant application, since it is apparent that further experimentation is required in order to determine the targeting sequences for the full scope of cytochrome p450 enzymes encompassed by the instant claims. Furthermore, additional experimentation would be required to identify the full scope of xenobiotic agents which induce the expression of the full scope of cytochrome P450 enzymes encompassed by the instant claims.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was

"ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Absent the need for further experimentation, no guidance is given in the specification as filed that would allow one of skill in the art to predict the structures of any other composition comprising antisense oligonucleotides possessing the claimed properties, since it is unknown what properties, structural or otherwise, that the antisense oligonucleotides of the present invention must possess for it to reduce the synthesis of a drug metabolizing cytochrome P450 enzyme that reduces the effectiveness of a drug. Additionally, although the instant claims are directed to a method, it is noted that the claimed methods require the use of a broad genus of compounds that are not sufficiently described in the specification as filed.

8. Claims 31-43 and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting cytochrome P450 antisense comprising the administration of the morpholino antisense oligomers targeting CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 or compositions comprising said antisense oligomers, does not reasonably provide enablement for practicing the claimed invention comprising the use of antisense oligonucleotides targeting any other mammalian cytochrome P450; moreover, although the specification is enabled for inhibiting the metabolism of drugs that are metabolized by CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and

CYP3A4, comprising the co-administration of morpholino antisense targeting these enzymes, does not provide enablement for altering the pharmacokinetics of any other drug (*i.e. those metabolized by other enzymes)* in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Although, the specification does demonstrate the efficacy of the antisense oligonucleotides according to SEQ ID NO: 18-20, 23-25, 35-36, and 46-47 that target CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYPC19, CYP2D6, CYP2E1, CYP3A2, and CYP3A4, in the working examples, no guidance or working examples are disclosed that would allow a skilled artisan to use antisense oligonucleotides to inhibit any other form of mammalian cytochrome P450 *in vitro* or *in vivo,* nor does the specification as filed teach that the above antisense oligonucleotides can be used to inhibit the metabolism of all drugs, or to alter the pharmacokinetic characteristics of any drug (as recited in claim 30). It is well known in the art that identification of target sites in a given mRNA at which antisense oligos bind to cause inhibition of translation is an unpredictable art. The skilled artisan would recognize that careful screening of oligonucleotides targeted to different sites on a given mRNA to find oligonucleotide binding sites for inhibition of translation, may fail to identify sites in the 5' untranslated region, the coding region, or in the 3'-untranslated region of the mRNA.

Applicant's own specification support the examiner's assertion of unpredictability in regards to both the design of effective antisense and their use to inhibit cytochrome p450 expression. For example, not that the specification demonstrates that several

antisense oligos were ineffective in inhibiting cytochrome P450 expression, for example oligos according to SEQ ID NO: 16-17 (see Table 6, and pages 29-30), 21-22 (see page 33, lines 9-11) and 37-38 (see page 28, lines 1-4) exemplify this point. Although these antisense oligomers were designed having a sequence complementary to a mammalian cytochrome p450, they did not produce any significant inhibition of the target enzyme.

There is a significant amount of unpredictability associated with the clinical application of antisense oligonucleotide therapeutics. Crooke (1999), states "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate." (page 5, lines 12-16) Furthermore, Crooke describes a variety of factors that influences the activity and behavior of antisense-based compounds. These factors include oligonucleotide purity, oligonucleotide structure, target RNA structure and RNA protein interactions, variations in cellular uptake and distribution, and binding to and effects of binding to non-nucleic acid targets (pages 3-5). Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, sequence of oligonucleotide and cell type. The effects of binding to non-nucleic acid targets may induce non-antisense effects that can be mistakenly interpreted as antisense or complicate the identification of an antisense mechanism. Additionally, such binding may also inhibit antisense activity of some oligonucleotides (page 5, 3rd paragraph). In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins, will be influenced by the chemical class of

oligonucleotide studied (page 5, 4th paragraph). Crooke clearly teaches that there is a significant level of factors, which influence the behavior of antisense based, compounds thereby rendering the activity of antisense compounds unpredictable.

Branch (1998) also teach that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNA molecules and their association with cellular proteins can render target sites totally inaccessible *in vivo*. Antisense therapy is a highly unpredictable field and the skill in the art is high.

According to Stein (2000) "[A]ntisense oligonucleotide biotechnology has entered a phase of its development in which many problems engendered by nonsequence specificity are being recognized and being actively addressed. However, in order to improve specificity of the methodology, attention must now also be paid to co-suppression of gene activity due to irrelevant cleavage." Stein further states that "[T]o the extent that this issue also is addressed, correlations between the down-regulation of a defined target and an observed biological outcome (e.g., growth suppression) eventually *[emphasis added]* may be possible." (page 235, Concluding remarks) Stein clearly suggests that use of antisense oligonucleotide therapeutics are highly

unpredictable due to "irrelevant cleavage" as a result of the low stringency requirements for RNAse H activity, wherein a 5-base complementary region of oligomer to target may be sufficient to elicit RNAse H activity (see Stein, abstract).

Crooke, Branch and Stein teach that the behavior of antisense based pharmaceuticals are unpredictable, therefore claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Additionally, Applicant's specification does not provide any evidence that the cytochrome p450 enzymes according to CYP1AA1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYPC19, CYP2D6, CYP2E1, CYP3A2, CYP3A4, and CYP6A1, recited in the instant claims are responsible for the metabolism of every known conceivable drug in general. Applicants have not recited, for example, the CYP3A5 P450 enzyme, the alcohol dehydrogenases, the acetaldehyde dehydrogenases, or the dihydropyrimidine dehydrogenase (see Ingelman-Sundberg, 2001, page 194, paragraph 2). *The instant claims broadly encompass the inhibition of the metabolism of any drug by means of co-administration of a morpholino antisense oligomer targeting the cytochrome p450 enzymes listed above.*

The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary therapeutic effect is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in

the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In view of the breadth of the claimed invention, specifically in regards to the method of inhibition of the metabolism of any generic drug, the lack of description in regards to the sequence of the broad genus of morpholino oligomers used in the claimed method, the lack of sufficient guidance in regards to the use of morpholino oligomers *in vivo*, the unpredictability associated with the behavior of an oligomer within a cell as it relates to the sequence composition of the oligomer, it is concluded that undue experimentation would be required to practice the full scope of the claimed invention, in particular using oligomers to inhibit the metabolism or alter the pharmacokinetics of drugs that are not metabolized by the mammalian cytochrome P450 enzymes of CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYPC19, CYP2D6, CYP2E1, CYP3A2, and CYP3A4.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 31-47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of issued US Patent No. 6,686,338. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and those of the issued US Patents are both drawn to a method of inhibiting the metabolism of a drug administered to a subject comprising co-administering with said drug a morpholino antisense oligomer to said subject.

The claims of the issued US Patents are drawn to methods comprising the administration of specific species of antisense oligonucleotides targeting a particular cytochrome P450 variant. However, the instant claims are drawn to a broad genus of antisense compounds used in the same methods which comprise administration of a morpholino antisense oligomer targeting cytochrome P450 in combination with a drug. Therefore since the scope of the claims of the instant application encompass the methods comprising the administration of the specific species of antisense oligomers

recited in the issued US patents, the claims of the issued US Patents are considered to anticipate the claims of the instant application.

Response to Arguments

9. Applicant's arguments filed 10/29/2007 have been fully considered but they are not persuasive. Specifically, Applicants argued that:

10. The claims satisfy the written description requirement. Applicants argued that knowledge of the nucleic acid sequence of the drug-metabolizing p450 gene and the corresponding transcript provides sufficient structural and functional information for a person of skill in the art to identify and design antisense oligonucleotide with the desired activity. Moreover, In the reply filed 10/29/2007, Applicants have relied heavily upon the Board Decision of Appeal No. 2005-2447 (*Ex parte Gleave)* as justification that the claimed invention fully meets the requirements of 112, 1st with regards to both enablement and written description. In this decision Applicant's were granted generic claims to methods of use of any antisense oligonucleotide which inhibits expression of IGFBP-5. Contrary to Applicant's assertions, although the claims in *Ex parte Gleave* were generic with respect to the structure of the antisense oligonucleotide, it is noted that the Board's Decision was based upon the disclosure that described antisense oligonucleotides targeting a distinct mRNA target, and claims directed to methods of using this distinct set of antisense oligonucleotides. In the instant case, Applicant's own disclosure support the examiner's assertion of unpredictability in regards to both the design of effective antisense and their use to inhibit cytochrome p450 expression. For example, note that the specification demonstrates that several antisense oligos were

ineffective in inhibiting cytochrome P450 expression, for example oligos according to SEQ ID NO: 16-17 (see Table 6, and pages 29-30), 21-22 (see page 33, lines 9-11) and 37-38 (see page 28, lines 1-4) exemplify this point. Although these antisense oligomers were designed having a sequence complementary to a mammalian cytochrome p450, they did not produce any significant inhibition of the target enzyme. Therefore, the decision in the *Ex parte Gleave* was based upon a distinct set of facts, and is not specifically applicable in the instant case.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Ford/
Primary Examiner
Art Unit 1633

JLE